ered here to express our reverence for the man and our admiration for the scholar. It is our part to keep alive the tradition of truth-loving, of scientific devotion and of perfect modesty which is our legacy from Joseph Leidy.

CHARLES S. MINOT

HEREDITY AND MICROSCOPICAL RESEARCH[1]

I have been much honored by the invitation to deliver the first lecture of a series established in honor of Joseph Leidy, a man distinguished alike for the diversity and importance of his original contributions to knowledge and for the far-reaching influence that he exerted on other men of science, in his own time and after. No American naturalist could be named whose biological interests ranged over a wider field; and the selection of my topic this evening has been influenced in some measure by the fact that Leidy was an almost solitary pioneer of microscopical investigation in this country, at a time when the cell-theory was in the earliest stages of its development, and when no one could have imagined the brilliant future that lay before it. Did time permit I would gladly dwell for a moment on his early observations on the structure and division of cells, and on the activities of the simplest forms of life. Much of his subsequent work lay in a very different field of inquiry, but his interest in microscopical investigation never deserted him, witness to which was borne by the publication in his later life of a beautiful monograph on the fresh-water rhizopods, which at once took its place as one of the classics of American zoology.

[1] A lecture delivered before the University of Pennsylvania, April 17, 1913, on the Joseph Leidy Foundation. With the exception of three general diagrams it has been impracticable to reproduce the figures that were shown by means of lantern slides.

More than half a century has passed since Leidy's earliest studies with the microscope. The main motive power behind the unparalleled advance in biology during this period has been the persistent effort to explain the activities of living things through investigations upon their structure, whether anatomical, physical or chemical. This effort entered upon a new era with the discovery of protoplasm and the promulgation of the cell-theory; for its final objective was now seen to lie in minute structural elements, the cells, of which the tissues are composed. Little by little it became clear that the cell, whatever else it be, is a microscopic chemical engine, where the energy of the foodstuffs is finally set free, and applied to the work of life. The question inevitably arose whether we can discover within the cell any visible apparatus by which this is accomplished. The inquiry has a thousand aspects; I ask your attention to that which relates to the problem of heredity.

It long since became clear that the cell-theory offers us a general explanation of heredity. Heredity is a consequence of the genetic continuity of cells by division, and the germ-cells form the vehicle of transmission from one generation to another. This fundamental discovery divested heredity of the mystery in which it had so long been enveloped, though it must always remain among the most wonderful of phenomena. But this result only cleared the way for further advances. Our scientific curiosity is aroused in the highest degree by more specific problems of heredity. Why do individuals now and then appear that show little resemblance to their immediate progenitors but "revert" to much more remote ancestors? Why do the grandparents often exert definite effects upon their grandchildren of which no suggestion is given by their children? What

explanation can be offered of the combinations and recombinations of parental or grandparental characters that appear in definite numerical proportions in hybrids? We may glance at a few particular cases that will serve to place some of these questions before you in more concrete form. In the first view we see the results of crossing two distinct races of sweet peas, each of which is pure white and produces only white offspring so long as strictly inbred. On crossing the two races the hybrids are always deep purple, like the wild Sicilian species, and in this respect they no doubt revert to an early common purple ancestor of the two white races. The offspring of the hybrids include a variety of purple, red and white forms, among which are whites that are identical with the two original grandparents. Here is a somewhat similar case in domestic fowls. You see two different white races, each of which breeds true; but when crossed together they produce deeply colored hybrids, showing a pattern of plumage that is closely similar to that of the wild jungle fowl from which both white races are probably descended. How is the reversion shown in this and the preceding case to be explained?

Let us look at some more complicated phenomena. We have here the result of crossing two differently colored races of fowls, the barred Plymouth Rock and the black Langshan. If the barred cock be paired with the black hen, all the offspring are barred, like the father. If the barred hybrids be paired together the progeny includes, on the average, three barred to one black, and the black bird *is always a female*. Quite different, and even more singular, is the reverse cross shown in the next view, where the black cock is paired with the barred hen. Half the offspring are now barred and half black; and the remarkable fact is that the barred birds are all males, the black ones all females. In color pattern the sons are like their mother, the daughters like their father—an example of the so-called "criss-cross" heredity. Upon pairing these hybrids together, the following generation (grandchildren of the original forms) includes males and females of both types, barred and black. In the following view we see a quite analogous form of heredity, observed by Morgan in crossing a long-winged and a short-winged race of fruit-flies (*Drosophila*). When the male of a long-winged race is paired with the female of a short-winged race, all the sons are short-winged like their mother, all the daughters long-winged like their father. On pairing these two, the offspring are of all four types, long wings and short wings occurring in both males and females.

Such results seem at first sight capricious, almost fantastic, but this first impression is erroneous. The results are not capricious, but constant. The experiments may be performed over and over again, always with the same result, so that the outcome may be unfailingly predicted in advance; and this demonstrates that such forms of heredity, and heredity in general, must be due to some definite apparatus in the germ-cells. I shall try to show that microscopical research has revealed to us at least something of the nature of this mechanism, and that it has practically solved some of the very puzzles that have just been propounded. In order to indicate the nature of this solution, I must first ask attention for a moment to the so-called "unit-characters" and their behavior in heredity, on which the attention of both cytologists and experimenters on heredity has been largely concentrated in recent years.

Unit-characters have become too familiar to require more than brief illustra-

tion. Examples of them have just been seen in the colors of flowers or of plumage, and in the structure of the wings in flies. Their interest lies especially in the fact that they are transmitted independently of one another, as if they were separate and independent things. By appropriate crossing experiments, such as we have just seen, particular groups of such characters may be split up and recombined, over and over again, in constantly new combinations, with no alteration of their individual character. Let us look at one or two examples of this. Here are the results of crossing two different races of wheat (from experiments by Biffen). One parent is a bearded variety with short, dense heads; the other a beardless form with long, loose heads. The hybrid is intermediate in shape, and is beardless. On pairing the hybrids together all combinations of the four original characters, and of the hybrid character, appear in the grandchildren, namely, (1) short beardless, (2) short bearded, (3) hybrid bearded, (4) hybrid beardless, (5) long bearded and (6) long beardless. These six types appear in definite numerical ratios, and it is evident that the bearded or beardless character has been transmitted quite independently of the shape of the head.

Another and very striking case of the same kind is here seen, again from Morgan's experiments on fruit-flies. The grandfather has white eyes and yellow body color; the grandmother red eyes and gray body color. In the first generation all the offspring have red eyes and gray color. Among the grandchildren, however, appear not only both the original combinations but two new ones, namely, white-eyed grays and red-eyed yellows. Here again the second generation of hybrids shows all possible combinations of the four original unit-characters, white eye, red eye, yellow color and gray color. With a larger number of unit-characters the same would hold true, but the number of combinations would be much larger.

We catch a glimpse here of the methods by which the modern breeder of plants or animals is able to break up known combinations and recombine them into new types, somewhat as the organic chemist splits up known organic compounds and recombines the products into new compounds, perhaps unknown before. Our ability to do this is often of high practical value. As de Vries has said, most hybrids owe their character to a new combination of qualities. "It is the combination that is new," he says, "not the qualities themselves. Some characters are derived from one parent, others from the other. Each of these may be simply inherited, . . . but by their new combinations they yield varieties of higher practical value, and notable examples are afforded in those cases where one parent has contributed vigor of growth, hardiness in winter, resistance to disease or productivity, and the other bright flowers, palatable fruit or nutritive seeds." An example of this which he cites is Luther Burbank's celebrated white blackberry, produced synthetically by uniting in one race the light color of the fruit of an inferior variety of cultivated bramble with the large and succulent fruit of the Lawton blackberry. Another familiar example, also cited from Burbank's work, is the so-called Shasta daisy, which unites the desirable qualities of plants from three different continents. An English daisy has contributed its large flowers and tall, stiff stems; a Japanese species its whiteness of bloom; an American field daisy its profusion of flowers and hardiness in winter. Many other examples might be given to illustrate how by disassociation, recombination and selection desirable qualities may be brought together and undesirable ones eliminated; and by

this principle the improvement of domestic races of plants and animals is being attempted in many parts of the world to-day.

Now, it is obvious that we should be able to understand the behavior of unit-characters, at least in some degree, if it could question how the splitting up and recombination of particular groups of such characters takes place. The main part played by microscopical research has been to bring forward proof that the hereditary characters are somehow connected with separate bod-

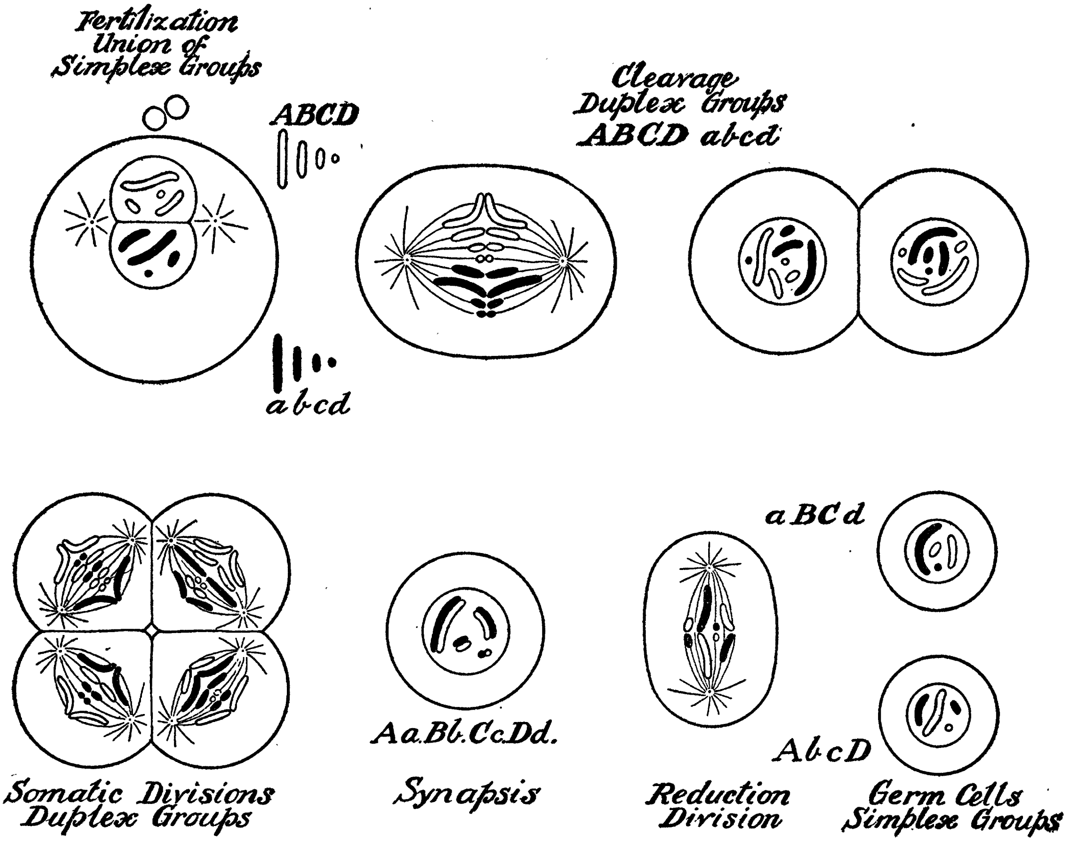

FIG. 1

be shown that they are somehow dependent individually upon separate structural elements or different chemical substances that may be separately transmitted through the germ-cells. It is just this which microscopical research and experimental researches on heredity, taken together, have demonstrated. They have accomplished more than this. They have not only shown with a high degree of probability how the transmission of unit-characters is effected, but have thrown at least some light on the ies, contained in or formed from the cell-nucleus, and known as the *chromosomes.* Besides the chromosomes the cell also contains another kind of bodies found in the cell-protoplasm, and known as *chondriosomes* or *plastosomes.* These too are very likely connected with heredity; but their true significance has not yet become very clear, and we shall hardly have time to consider them within the limits of this address.

With the aid of the accompanying diagram (Fig. 1) we may consider a few es-

sential facts concerning the chromosomes, leaving aside most of the complicated technical details. In each species of plant or animal the chromosomes are of constant, or nearly constant, number. They divide as the cell divides, and are thus transmitted from cell to cell. In the fertilization of the egg two similar groups of chromosomes are brought together, one contributed by the egg, one by the sperm-cell; and as the egg step by step divides to build up the body of the embryo the chromosomes also divide at each cell-division. Every cell-nucleus thus receives a double group of chromosomes, consisting of two single groups descended respectively from the two groups that originally came together in the fertilized egg. The two single groups of each nucleus are thus of maternal and of paternal ancestry, respectively. This all-important conclusion has been obstinately contested and is still denied by a few writers. I think, however, that all arguments against it must give way before the fact that in certain hybrids—in particular, certain fish-hybrids observed by Moenkhaus—the chromosomes of maternal ancestry can actually be distinguished by the eye from those of paternal. Finally, when new germ-cells are produced for the formation of the following generation the double chromosome-groups are again reduced to single ones in preparation for the succeeding process of fertilization.

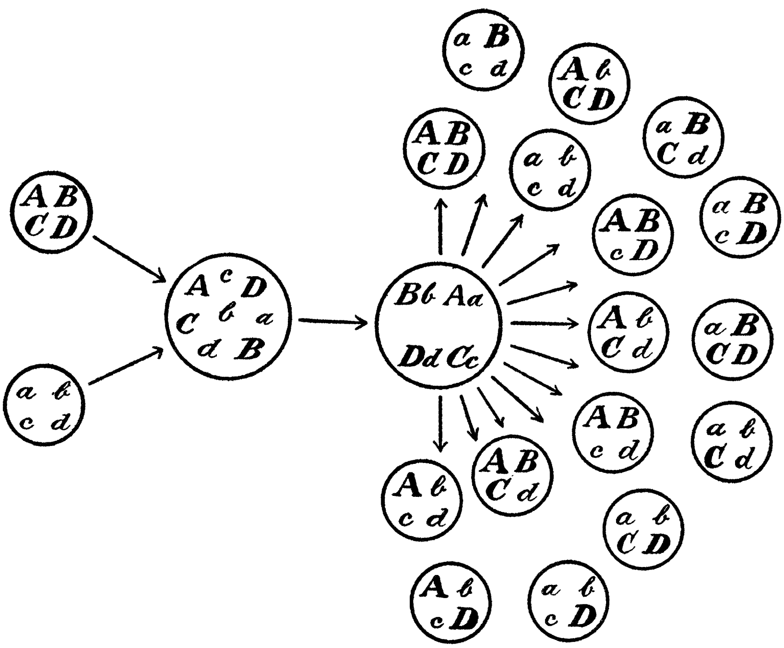

FIG. 2

These are not theories but observed facts. It is impossible to overlook the very precise parallel which they show to what Gregor Mendel and his successors have proved to be true also of the unit-characters, as will be made clear by the accompanying diagram (Fig. 2). When two similar or nearly similar individuals unite in fertilization they contribute to the germ two corresponding groups of unit-characters, which are designated in the diagram by two series of letters A–D and a–d, respectively. The

offspring are therefore of double or "duplex" hereditary constitution. When the germ-cells are formed, as Mendel first proved by experiments on hybrids, they are found to carry only a single or "simplex" group of characters. So closely parallel is all this to what we have learned about the chromosomes that we can just as well use the diagram for the chromosomes as for the characters. Chromosomes and characters alike form a single or simplex group in the germ-cells, a double or duplex group in the body of the offspring; and this alone is sufficient to make it extremely probable that chromosomes and characters are somehow connected. Exactly what is the nature of this connection we are not able to say with certainty; but we might reasonably assume, for instance, that each character depends upon some particular chemical substance, or group of substances, contained in the chromosomes, and that different chromosomes differ in respect to the substances which they carry. Such an assumption would be thoroughly in accord with the principles of chemical physiology and with the results of experiments upon the physiology of development.

The diagram brings out another fundamentally important fact that was also proved by Mendel's experiments, namely, that in the formation of the simplex character-groups all possible recombinations of the original parental unit-characters (within the limits of a single complete group) are effected. Only a few of the germ-cells receive the original combinations unchanged (A–D or a–d). In most cases new simplex groups are formed by recombination, such that each germ-cell receives always a complete single series (from A or a to D or d), but any particular member of the series may be derived from either parent. The number of such possible combinations varies, of course, with the simplex number of unit characters; with 4 characters, as in the present case, it is 16; with 15 characters it would be more than thirty thousand. Any individual may thus produce many different kinds of germ-cells, equivalent in a general way but differing slightly in respect to their individual hereditary components. This result follows from the fact, discovered by Mendel again, that corresponding or homologous parental components of the duplex groups (such as A and a, or B and b) never enter the same germ-cell; and this is the essential fact in "Mendel's Law." We could readily understand this if before the germ-cells are formed corresponding parental components become associated in pairs (Aa, Bb, etc.) and then separated or disjoined in an ensuing process of division. If the process of disjunction took place in each pair independently of the others, all combinations would obviously be produced in the resulting germ-cells. Now, it is certain that something like this actually takes place in the case of the chromosomes. In the process known as *synapsis,* which takes place shortly before the last two cell-divisions concerned in the formation of the germ-cells, the chromosomes do in fact unite in pairs, two by two. There is reason to believe that the two members of each pair are respectively of maternal and paternal derivation; and the probability of this view, first stated by Montgomery, has steadily increased. Observation has made it extremely probable that in the course of the following two divisions the two members of each pair, or two somethings that they contain, are separated so as to pass into different germ-cells (Fig. 1). One of the most interesting recent discoveries in cytology is the fact that in some animals and plants a paired arrangement of the chromosomes is assumed long before the period

of synapsis, and may even be seen more or less distinctly throughout the life of the organism.

As has been said, the remarkable parallel between chromosomes and unit-characters constitutes in itself strong (though indirect) evidence that the latter depend in some way upon the former. Specific experimental evidence directly demonstrates the correctness of this conclusion. If, for instance, the orderly distribution of the chromosomes in the fertilized egg is artificially interfered with (as may be done in several ways) the development of the embryo is correspondingly disturbed. Boveri has proved that when abnormal combinations of the chromosomes are thus produced in the fertilized eggs of sea-urchins the offspring are almost always abnormal, deformed or monstrous. Recent experimental studies have proved by various methods that certain interesting abnormalities shown in hybrids are preceded by corresponding disturbances in the chromosomes. Again, it is now possible to fertilize the eggs of such animals as sea-urchins by the spermatozoa of animals as widely different as worms or mollusks. The offspring of such "heterogeneous" crosses show only the characters of the mother. They are typical sea-urchin larvæ; and the explanation, demonstrated by microscopical observation, is that only the chromosomes of the mother are able to survive in the fertilized egg. Those of the foreign father (*i. e.*, of the sperm cell) sooner or later perish and degenerate within the egg.

Still another fact, of the same unmistakable import, is the recently demonstrated relation between the chromosomes and sex. Sex is now definitely known to be inherited like other characters; and within a few years the decisive proof has been attained that the heredity of sex is connected with a particular chromosome known as the "sex-chromosome" or "X-chromosome." In a large class of cases, to which man almost certainly belongs, the male contains but one of these chromosomes, the female two; hence in such cases the total number of chromosomes in the female is one greater than in the male. In respect to these particular chromosomes, accordingly, the male always remains of simplex composition (XO), while the female is of duplex (XX). Observation has proved further than when the duplex chromosome-group of the female are reduced to simplex ones each mature egg retains a single X-chromosome, while in the male only half the spermatozoa receive X and half do not. From this it follows that when the egg (X) is fertilized by a sperm-cell containing X the result is a female (XX), while if fertilized by a sperm-cell without X, the result is a male (XO). I shall try to show a little later how clearly and simply these facts explain certain very curious special phenomena connected with the heredity of sex.

The specific and direct evidence thus briefly outlined has definitely established the fact that the chromosomes are causal agents in heredity; and it has already become evident that the study of their modes of distribution, combination and recombination provides us with a key which will unlock many special puzzles of heredity which would otherwise seem to us insoluble. I will attempt to make this clear in greater detail by considering three of the particular cases that have already been touched upon, taking them up in the order of their difficulty.

The simplest of these cases is that of reversion, illustrated by the sweet peas. It is evident from the experimental results that the purple color of the flowers requires the cooperation of at least two things, either of which alone is unable to produce

any color. These two things may for the moment be called "A" and "B." Both A and B must obviously have been present in the original purple race from which the two white races are descended. One race has at some time in its past history lost A, the other B; and each loss has produced a specific type of white race which breeds true. By crossing the two A and B are again brought together, thus restoring the original combination AB; hence the "reversion" to the purple wild type. Now, the things which we have called "A" and "B" may very well be different chemical substances. If we assume them to be borne by different chromosomes, brought together in the hybrid, the whole matter becomes at once clear and simple. It seems probable that all kinds of reversion may be explained by the same principle.

The second case is that of "criss-cross" heredity in the short- and long-winged flies, where the sons are like their mother, the daughters like their father. The explanation of this case is less easy to follow than that of reversion, but is more specific. This case, and many others of similar type, may be completely explained through our knowledge of the relation of the chromosomes to sex. These flies agree with the general rule already referred to, that the males contain a single X-chromosome, or sex-chromosome, the females two. All the facts revealed by experiment are very simply and completely accounted for by the single assumption that the X-chromosome is responsible not only for sex, but also for the short-winged character. Specifically, the assumption is that the short wings are due to the lack or defect of something (let us again say some definite chemical substance) that is contained in the X-chromosome. Let us see just how this works out. We may write the formula for the short-winged female as xx (the small letters indicating the defect in X that is responsible for defective wing development), while that of the normal (long-winged) male is XO. Such a female produces eggs of only one type, x, while the normal male produces sperms of the two types X and no X or O. Fertilization thus can only give rise to the two combinations xX and xO, the former being females, the latter males. The males are short-winged because they contain only the defective x. The females likewise contain such an x, but they are nevertheless long-winged because they also contain a normal X, which is sufficient to ensure normal wing development. It follows that the daughters are long-winged like their father, the sons short-winged like their mother. I need not trace this explanation further into its details. It is enough to say that upon this one assumption the results of many other kinds of crosses among these flies work out perfectly; and a similar explanation will completely account for other cases of criss-cross fertilization, for such curious phenomena as the heredity of color-blindness in man, and many other cases in which particular somatic characters are linked with sex in a definite way. These cases offer, indeed, a brilliant example of the clearness and simplicity of the causal explanations that microscopical research has helped to give of complicated special phenomena of heredity.

As a third and last example I select an even more interesting and instructive case, the complete analysis of which carries us to the firing line of research in this field. It illustrates the influence of the grandparents upon the combinations of unit-characters seen in the grandchildren. It is a very curious fact, only recently discovered, that in certain cases hybrids of identical composition exhibit marked differences in their output of offspring that can

only be explained by an exact knowledge of the grandparents. We have already seen a concrete example of this; but before returning to it the essential result may be explained by means of a diagram. Let us consider the case of a hybrid that contains four characters, which we will designate as A, a, B and b. The hybrid AaBb can be made in two ways, according to the composition of the parents. First, one parent may contribute AB and the other ab; or, secondly, one parent may contribute Ab and the other aB. These two crosses seem to give precisely the same result, AaBb. The hybrids produced by the two methods look exactly alike; they produce the same kind of offspring (grandchildren of the original forms). The remarkable fact is, however, that in some cases (probably in many) the offspring of the two kinds of hybrids differ in respect to the numerical proportions in which different combinations of the grandparental characters appear. In both cases the grandchildren are of four visibly different types, AB, aB, Ab and ab. Following the first cross, however (AB $\times$ ab), the classes AB and ab are in great excess among the grandchildren, sometimes in very great excess; while following the second cross (Ab $\times$ aB) it is the classes Ab and aB that are in excess. In other words, in each case a large majority of the grandchildren are of the same type as their grandparents, while a small minority show new combinations of the grandparental characters. To change the statement, if A and B enter the hybrid together they tend to come out together in the grandchildren; if they enter separately they tend to come out separately. Why should this be so?

The facts will become clearer if we look again at the actual case of the fruit-flies already referred to, which was worked out by Professor Morgan. The grandfather combines white eyes and yellow body color; the grandmother red eyes and gray color. White eyes and yellow color here enter the hybrid together, while white eyes and gray color, or red eyes and yellow color enter separately. The hybrids in the first generation all show red eyes and gray color, like the mother. On pairing the hybrids together, all four combinations appear—red eye and gray color, white eye and yellow color, white eye and gray color and red eye and yellow. The last three of these are *seen* only among the males; for although also present among the females they do not come into actual view, because in this sex white eye or yellow color is dominated or concealed by red eye or gray color. We may therefore confine our attention to the males. Now, on counting the relative numbers of these types among the grandsons a remarkable result constantly appears. An enormous majority of them—more than 100 to 1—show the same combinations as the grandparents, namely, white eye and yellow color, or red eye and gray color; while the two new combinations, white eye and gray color, and red eye and yellow color, are correspondingly rare. This, I repeat, is obviously because the characters that enter the hybrid together tend to come out together in the grandchildren; those that enter separately tend to come out separately. This at once suggests that the difference of result depends upon whether the two characters in question are borne by a common carrier in the germ-cells or by different carriers. White eye and yellow color tend to hold together because they enter the hybrid in some common carrier. White eye and gray color, or red eye and yellow color tend to remain separate because they enter the hybrid in different carriers. What are these carriers? Very extended experiments, analogous to that just de-

scribed, and involving the breeding of many thousands of these flies, have steadily increased the probability that these carriers are nothing other than the chromosomes. These experiments make it almost certain that in the cross we have been considering white eyes and yellow color are alike determined by the same chromosome, while red eyes and yellow color must obviously have been carried originally by different chromosomes, since they came from different grandparents.

There is here, as in the case of the short-winged flies, almost conclusive proof that a single chromosome may be responsible for the heredity of more than one character; and experiments of the same type have proved that a single chromosome may be responsible for many characters—at least twenty, and probably many more. Independent microscopical investigation has provided a very definite basis for this conclusion, having made it almost certain that the chromosome is a compound body, which includes many smaller elements, perhaps different chemical substances, each of which may play a definite part in determination. Both kinds of evidence indicate that these different elements are arranged in the chromosomes in linear series and in a definite way. The chromosomes arise from long threads, which split lengthwise throughout their whole length during division. In this way all the separate elements or substances which they contain may be equally divided and distributed to the daughter cells.

And this leads us finally to one more point that now forms a center of interest in these studies. Although (in such cases as we have been considering) characters that enter the hybrid together tend to come out together in the grandchildren, they do not always do so. As we have seen, in a few of the grandchildren characters that were originally associated have separated so as to produce new combinations—such, for example, as the white-eyed gray flies, or the red-eyed yellows. How can this be reconciled with the conclusion that they were originally borne by the same chromosome? A possible answer to this question has been offered by Janssens's theory of the "chiasmatype," which has been more specifically and very ingeniously worked out by Morgan and some of his pupils. Reference has already been made to the fact that at a certain period, shortly before the germ-cells are formed, corresponding maternal and paternal chromosomes become coupled in pairs, side by side (synapsis). This process is always followed by a more or less intimate union of the two threads, perhaps in some cases by actual fusion. The evidence is still more or less conflicting as to exactly what follows; but it is certain that at a later period two separate and parallel threads again become distinct, and these *may* separate so as to pass unchanged into different germ-cells. These two threads are believed by many observers to be identical with those that originally united in synapsis, but this is in dispute. The fact of particular interest in this connection is that the two threads often become twisted around each other like the strands of a rope; and the observations of Janssens indicate that in some cases these threads may fuse at certain points where they cross and then split apart at these points in the longitudinal plane. By this process, as will be made clear by the accompanying diagram (Fig. 3), the possibility is given of an *orderly* exchange of certain regions of the threads between the two chromosomes of each pair. Now, it has been suggested that in this way two chromosomes that originally carry (let us say) AB and ab, may undergo such an exchange as to produce the new chromo-

somes Ab and aB, as shown in the upper part of the diagram. If this should happen only occasionally it would fully explain how it is that two characters borne by the same chromosome tend to remain together, yet *may* separate so as to pass into different chromosomes and hence into different germ-cells. As shown in the lower part of the diagram, a similar explanation may be extended to much larger series of characters, the behavior of which in detail may depend upon their arrangement in the threads, or on the character of the twisting. On the basis of this hypothesis an attempt has recently been made by Sturtevant to calculate from the observed results the degree and character of the twisting of the chromosomes, and the relative position of the different specific elements within them. This, admittedly, is a bold venture into a highly hypothetical region. Its justification is the pragmatic one that it "works." The hypothesis gives us the only intelligible explanation that has yet been offered of a series of undoubted facts; and it is certainly worthy of the most attentive further examination.

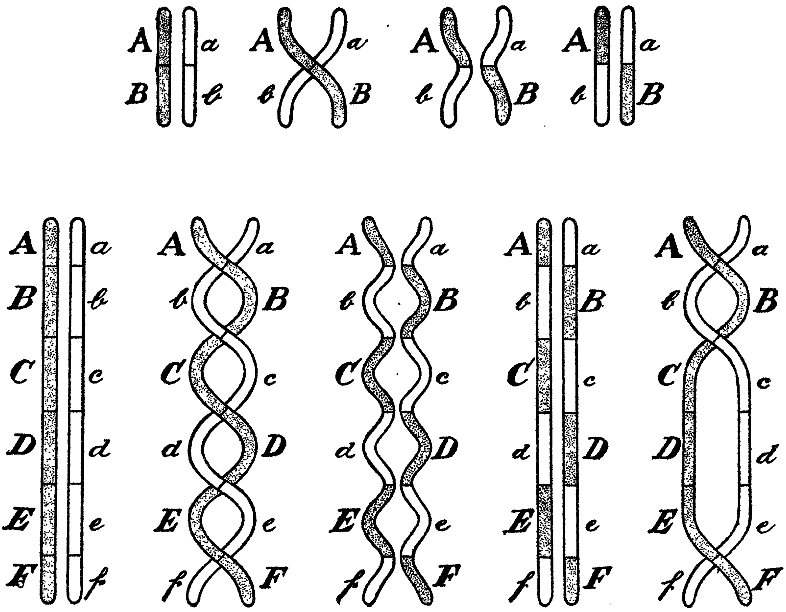

FIG. 3

The three cases that have been considered have led us, step by step, to the border line of research in this field. I have not hesitated, in discussing the last case, to advance beyond the solid ground of observed fact into a debatable and hypothetical region; for it is by just such venturesome advances that new possibilities of discovery are opened. We have much to gain and nothing to lose by the use of explanatory hypotheses that are naturally suggested by the facts and help us to formulate them for analysis, so long as such hypotheses are not allowed to degenerate into dogmas accepted as an act of faith, but are only used as instruments for further observation and experiment. The "chiasmatype" hypothesis is no more than this; and though it is directly suggested by observed facts it remains for the present unproved. The more general conclusions that have been indi-

cated regarding the chromosomes stand, however, upon much firmer ground. That the chromosomes are in fact causal agents in determination can now be doubted, so I think, only by those who refuse to reckon squarely with the whole body of evidence. That the distribution of the chromosomes, or of smaller elements that they contain, gives us at least a partial explanation of the behavior of unit-characters has become in a high degree probable. The stubbornness with which each step in the establishment of these conclusions has been contested has been largely due, I think, to a misapprehension for which the advocates of the chromosome-theory are themselves in part responsible. The chromosomes have often been spoken of as if they were central, controlling factors in heredity, or as if they were actual bearers of the unit-characters—the latter form of expression has in fact been employed, for the sake of brevity, in the foregoing discussion. But it seems to me that such expressions are, to say the least, misleading; they are certainly unnecessary. It is perfectly obvious that chromosomes do not bear hereditary characters as such; they bear only *somethings* that are necessary to the production of characters. I again repeat that these "somethings" may be at bottom of chemical nature. We find it convenient, in order to avoid circumlocution, to speak of these things or substances as "determiners"; and there is no objection to doing this so long as we do not forget that many other things are concerned in the production of every character. Experiment has made it certain that the cell protoplasm is thus concerned. It is possible that the chondriosomes or plastosomes may here play an important part. In any case, the conclusion is not to be escaped, I think, that the whole cell-system is directly or indirectly involved in the production of every hereditary trait. To treat the chromosomes as if they were central governing or controlling factors in the cell is a procedure of more than doubtful expediency. For the present, at least, all the requirements of investigation are sufficiently met if we think of the chromosomes, or that which they carry, only as *differential factors* in heredity, not as its primary or exclusive "determiners." Whether they possess a significance more fundamental than this is a question that may well await the results of further inquiry.

I can refer here to only one or two of the many disputed questions of detail regarding the chromosomes. One of the most important is whether the chromosomes retain their individuality intact in the nuclei of the "resting period" or interkinesis that intervenes between successive cell-divisions. Some of the most careful recent cytological studies in this direction seem to show that such is not the case. Nevertheless these same studies, together with recent experimental evidence, give very strong ground for the conclusion that a definite relation of genetic continuity exists between the individual chromosomes of successive generations of cells. On the one hand, the cytological studies of Boveri, Bonnevie, Vejdovsky and others, almost conclusively prove in certain cases that each chromosome is formed directly from the substance of a corresponding chromosome in the preceding generation. On the other hand, cytological and experimental evidence combine to show that alterations of the chromosome-groups, involving the addition to or subtraction from the group of one or more *particular chromosomes,* are perpetuated generation after generation of cells, even throughout the life of the individual. Nature performs such an experiment every day in the production of sex; for the particular chromosome-com-

binations established by the entrance into the eggs of spermatozoa with or without the X-chromosome persist throughout the whole development of the individual until new germ-cells are formed.

A second fundamentally important question, concerning which no general consensus of cytologists has yet been reached, relates to the mode of union of the chromosomes in synapsis and the subsequent distribution of their substance to the germ-cells. Only in a few special cases has complete proof been attained of a conjugation followed by complete disjunction or separation of the original conjugating chromosomes. Until this complicated and difficult problem has been much more thoroughly studied we shall not be in a position to explain exactly what is the mechanism of Mendel's law of heredity and the distribution of the unit-factors to the germ-cells. We are not dealing with a closed chapter in the study of heredity. Both genetic and microscopical research are still in a formative stage. It is hardly a decade since they finally converged upon the same specific problems. We must not yet make too exacting a demand upon the explanatory capacity of either; and it is a part of the present interest of the subject that so much still remains to be accomplished.

We have thus arrived at some of the most advanced and difficult questions in this field of inquiry. Perhaps I have not succeeded in making entirely clear even the few illustrative cases that have been considered. If so, I must plead in extenuation that the subject is beset with technical difficulties; and we biological folk have come to speak a language that is strange to many of our fellows. But I have been less concerned with the presentation of particular results or the critical discussion of details than with the indication of a point of view; I have only wished to point out one of the pathways along which students of cytology are attempting to cooperate with students of genetics in their attack upon the problems of heredity. I would like to urge in closing that such explanations as have here been briefly indicated are not mere vague and general notions. They are specific and detailed interpretations of observed facts. They enable us, up to a certain point, to comprehend what goes on in the germ-cells, to form perfectly clear mental pictures of the apparatus of heredity, and of its mode of action in particular cases. They contain no mystical or transcendental element. I repeat that they are entirely in accord with the principles of chemical physiology, and with the experimental results upon the physiology of development. To this extent at least the explanations are real and represent a partial solution of the problem of heredity. No one would maintain that these explanations are final. I do not doubt that with advancing knowledge we shall in time come to look back upon many of our present conceptions as crude and naïve. Discovery in this great field of research has made no approach to its limit. Great progress in the future is certain. But if you ask whether we may hope to reach at last a complete or final solution of the problem of heredity, I fear the answer must be, no. The man of science should be the first to admit that science can not attain to a complete understanding of anything. The explanation of any phenomenon only uncovers new phenomena behind it that still demand explanation, in endless succession; and such is the essential characteristic of scientific progress. Science does not aim at ultimate explanations; and could we find them, science would be emptied of its interest to the investigator.

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